Accepted Manuscript

Letter to the Editor: First-in-Man Randomized Clinical Trial of Renal Denervation for Atrial Arrhythmia Raises Concern

Jan A. Staessen, MD, PhD Yu Jin, MD, PhD Lutgarde Thijs, MSc Alexandre Persu, PhD Michel Azizi, MD, PhD Sverre Kjeldsen, MD

PII: S0735-1097(13)05309-6

DOI: 10.1016/j.jacc.2013.07.095

Reference: JAC 19428

To appear in: *Journal of the American College of Cardiology*

Received Date: 8 July 2013

Accepted Date: 9 July 2013

Please cite this article as: Staessen JA, Jin Y, Thijs L, Persu A, Azizi M, Kjeldsen S, Letter to the Editor: First-in-Man Randomized Clinical Trial of Renal Denervation for Atrial Arrhythmia Raises Concern, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.07.095.

Letter to the Editor: First-in-Man Randomized Clinical Trial of Renal Denervation for Atrial Arrhythmia Raises Concern

Short title: Concern about NCT01117025

Jan A. Staessen, MD, PhD, Yu Jin, MD, PhD, Lutgarde Thijs, MSc, Alexandre Persu, PhD, Michel Azizi, MD, PhD, Sverre Kjeldsen, MD,

Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium (Y.J., L.T., J.A.S.); Department of Epidemiology, Maastricht University, Maastricht, The Netherlands (J.A.S.); Institut de Recherche Expérimentale et Clinique and Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (A.P.); Université Paris Descartes, Faculté de Médecine, F-75005 Paris, France (M.A.); Department of Cardiology, Ullevål University Hospital, University of Oslo, Oslo, Norway (S.E.K.).

Corresponding Author:
Jan A. Staessen
Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, block D, Box 7001, BE-3000 Leuven, Belgium.
+3216347104
+3216347106 (fax)
E-mail: jan.staessen@med.kuleuven.be or ja.staessen@maastrichtuniversity.nl

Disclosures: S.E.K. received honoraria for lecturing from Astra-Zeneca, Bayer, Medtronic, Merck Sharp & Dohme, and Takeda, and consulting honoraria from Bayer, Medtronic, Takeda and Serodus, and grant sup-port from Astra-Zeneca. M.A. was investigator in the Simplicity HTN2 and the Reduce-HTN trials and received consulting honoraria from Boston Scientific, Vessix and Cordis. None of the other authors declares a conflict of interest.

Pokushalov and colleagues reported the first-in-man randomized clinical trial (NCT01117025) comparing the effects of pulmonary vein isolation with (intervention) or without (control) renal denervation in patients with refractory atrial fibrillation and treatment-resistant hypertension (1). We were struck by several inconsistences in this trial.

First, of particular concern are the changes in design, primary endpoint, sample size, and inclusion and exclusion criteria from the successive protocols posted at http://www.clinicaltrials.gov (see Supplementary Material available online) to the published report (1). The original protocol identified office systolic blood pressure at 2 years – not recurrence of atrial fibrillation at 1 year – as the primary endpoint that should have informed the sample size calculations. The number of patients actually randomized was 27 (1), one more than required according to last version of the protocol at the registry website, and 82% less than first planned for (n=150). The discrepancy is especially worrisome, because the P-value for the between-group difference in the incidence of atrial arrhythmia was only 0.033 (1), so that adding a single control patient (14 instead of 13) might have made the statistical significance. The results of atrial ablation in the control group were dismal (2). Previous use of amiodarone was an exclusion criterion in the published paper (1), but not in any version of the design in the trial registry. The original exclusion criterion of secondary atrial hypertension was changed into secondary hypertension without mention of the diagnostic procedures. At variance with the CONSORT statement (3), the number of patient screened and invited remains unreported (1).

Second, Pokushalov's trial was registered as investigator driven without industry sponsor. Researchers were originally located in Novosibirsk and Athens. An employee from industry coauthored the published report (1). The group, who first published on the blanking period (4) and

also received industry support (1), was also added at the publication stage. Pokushalov excluded the first 3 months after pulmonary vein isolation from the analysis of recurrent atrial fibrillation (1). This so-called blanking period (4) should not have been longer than 2 to 4 weeks, because recurrence of atrial fibrillation significantly declines after 1 month and thereafter remains stable (5). Moreover, all of Pokushalov's patients were treated with propafenone or flecainide for 6 weeks after the procedure (1).

Third, the published methods (1) are not detailed enough to allow an independent replication of the study. The catheter used to stimulate the renal nerves is not mentioned. An exhaustive internet search for the Stimulator B-53 led us to http://www.biotok.ru. This company is currently located in Tomsk, not in Saint Petersburg. We could not access their website, because of an HTTP 500 Internal Server Error. Furthermore, Pokushalov's paper does not provide any information on the technique or reproducibility of the echocardiographic measurements (1).

Fourth, there are possible differences between described and applied statistical methods. The authors stated that continuous variables were presented as mean±SD and analyzed by *t* test (1). Systolic/diastolic blood pressure averaged 178±8/96±4 mm Hg in 14 control patients and 181±7/97±6 mm Hg in 13 patients of the intervention group. For the blood pressure level, SDs around 8 mm Hg systolic and 5 mm Hg diastolic seem unrealistic, unless patients were selected within narrow blood pressure limits. Reportedly, in the interventional group, the fall in blood pressure at 12 month averaged -25±5 mm Hg systolic and -10±2 mm Hg diastolic (1), while the change read from Figure 5 (1) was -25±3 mm Hg systolic. Recalculation of the *P*-values, using an unpaired *t* test and the blood pressure changes digitized from Figure 5, showed that the measure of spread for both blood pressure and blood pressure fall was probably not SD, but more

likely SE. For comparison, in the SYMPLICITY HTN-2 study (6), office blood pressure (±SD) averaged 178±16/98±17 mm Hg in the control group (*n*=52) and 178±18/97±16 mm Hg in the renal denervation group (*n*=52), and the blood pressure changes at 6 months (±SD) were 1±21/0±10 mm Hg in the control group and - 32±23/12±11 mm Hg in the denervation group. SD is not dependent on sample size, whereas SE is.

Fifth, Pokushalov and colleagues (1) did not report key test statistics and rounded measures of central tendency and spread to a single meaningful digit. In a parallel-group trial, *P*-values for the within-group changes in an outcome variable provide some information, but the main test statistics should rest on baseline-adjusted between-group differences in the endpoint. Pokushalov did not show these key statistical parameters (1). Furthermore, the echocardiographic results were not consistently reported throughout paper. Table 1 shows baseline values only for left atrial diameter and left ventricular ejection fraction (1). Next, Table 2 gives changes from baseline in thickness of the interventricular septum, posterior wall, left ventricular internal diameter and left ventricular mass index, of which baseline values were not given (1). Moreover, echocardiographic measurements were expressed in unusual units: centimeter instead of millimeter for the interventricular septum, the posterior wall and the left ventricular internal diameter, and g/m, not g/m^2, for left ventricular mass index. This issue is not trivial, as the changes in left ventricular walls and internal diameter were small with average within-group changes ranging from 0.1 to 1 millimeter. Rounding measures of central tendency and spread to a single meaningful decimal and reporting left ventricular echocardiographic measurements in centimeters rather than millimeters makes it difficult to reproduce *P*-values from the published data.

Sixth, one other potential inaccuracy pertains to the number of drugs taken. According to Table 1 (1), the number of antiarrhythmic drugs averaged 3.6 (range, 2 to 5) in control patients and 3.8 (range, 2 to 5) in the intervention group. The number of antihypertensive drugs was the same, albeit with different ranges as reported in the Results: 3.6 (range, 3 to 5) and 3.8 (range, 3 to 5), respectively. The use of 5 antiarrhythmic drug in a single patient, is incompatible with current guidelines (7).

According to Ioannidis' seminal essay (8), several corollaries for a possible false result might apply to Pokushalov's study (1). The likelihood that research findings are true decreases with smaller sample size (corollary 1); greater flexibility in designs, definitions, outcomes, and analytical methods (corollary 4); greater financial or other interests and preconceived ideas in a scientific field (corollary 5); and hotter research topics (corollary 6). In conclusion, the methodological drawbacks in Pokushalov's report (1) cast doubt on its validity, which clearly does not comply with CONSORT standards (3). Our observations highlight the necessity to have the design, methods, statistics and conclusions of Pokushalov's report revised (1) and to continue remaining vigilant about the peer-review process.

References

1. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparisonof pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 2012; 60:1163-70.

2. Verdino RJ. Catheter ablation for the treatment of atrial fibrillation. Have we been targeting the wrong organ? J Am Coll Cardiol 2012; 60:1171-2.

3. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet 2008; 371:281-3.

4. Joshi S, Choi AD, Kamath GS, et al. Prevalence, predictors, and prognosis of atrial fibrillation earky after pulmonary vein isolation : findings from 3 months of continuous automatic ECG loop recordings. J Cardiovasc Electrophysiol 2009; 20:1089-94.

5. Link MS. What is the "Blanking Period"? J Cardiovasc Electrophysiol 2009; 20:1095-6.

6. Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial) : a randomised controlled trial. Lancet 2010; 376:1903-9.

7. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33:2719-47.

8. Ioannidis JPA. Why most published research findings are false. PLOS Medicine 2005; 2:e124 (DOI 10.1371/journal.pmed.0020124).